Stroke Prevention with the Expanded Use of NOACs

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Treatment vs. Prevention

• 750,000 strokes per year in U.S.

• How many can get acute treatment?

• 100% can get secondary prevention
The Problem: Stroke Prognosis

Years Following Ischemic Stroke

Risk of Event

Recurrent Stroke

MI or Fatal Cardiac Event

MS Dhamoon *Stroke* 2006;66:641
TIA/Stroke Evaluation and Prevention

What is the cause of the TIA or stroke?

Prevention depends on it!
Ischemic Stroke Subtypes

NINCDS Stroke Data Bank:

German Stroke Data Bank
Cardioembolism
Therapeutic Range for Warfarin Balancing Safety and Efficacy

RE-LY Trial
Dabigatran for Stroke Prevention in Atrial Fibrillation

Non-valvular atrial fibrillation at moderate to high risk of stroke or systemic embolism (at least one high risk factor)

Warfarin
1 mg, 3 mg, 5 mg (INR 2.0-3.0)
N=6000

Dabigatran
Etexilate
110 mg bid
N=6000

Dabigatran
Etexilate
150 mg bid
N=6000

Primary objective: Noninferiority to warfarin
Primary end point: Stroke + systemic embolism
Minimum 1 year of follow-up, maximum of 3 years and mean of 2 years of follow-up
Stroke or Systemic Embolism
Dabigatran: Major Bleeding

Compared to warfarin:
D110: RR=0.80; 95% CI, 0.69-0.93; $P=0.003$ *
D150: RR=0.93; 95% CI, 0.81-1.07; $P=0.31$
Dabigatran

• Dabigatran 150 mg bid
  – reduces the risk of stroke and systemic embolism by \( \sim 25\% \) compared to warfarin
  – risk of major bleeding is similar to warfarin

• Dabigatran 110 mg bid
  – about the same efficacy as warfarin
  – risk of major bleeding about 20\% lower than warfarin
  – (not approved in U.S.)
ROCKET-AF: Rivaroxaban

- AFib and at high risk for stroke
- Randomized 14,264 subjects
  - Rivaroxaban 20 mg once daily
  - Warfarin to INR 2.0-3.0
- Primary Outcome: stroke and non-CNS embolism
Rivaroxaban: Similar Risk of Stroke or Systemic Embolism

HR 0.88 (0.74-1.03), p<0.001 for non-inferiority, p=0.12 for superiority
Rivaroxaban: Similar Major Bleeding

Compared to warfarin:
Rivaroxaban: 1.04 (0.90-1.20); p=0.58
Rivaroxaban

- Rivaroxaban non-inferior to warfarin for prevention of stroke and non-CNS embolism
- Similar rates of bleeding with both, but less ICH and fatal bleeding with rivaroxaban
ARISTOTLE: Apixaban vs Warfarin

- **Inclusion risk factors**
  - Age ≥ 75 years
  - Prior stroke, TIA, or SE
  - HF or LVEF ≤ 40%
  - Diabetes mellitus
  - Hypertension

- **Primary outcome**: stroke or systemic embolism

- **Randomize double blind, double dummy**
  - *(n = 18,201)*

- **Apixaban 5 mg oral twice daily**
  - *(2.5 mg BID in selected patients)*

- **Warfarin** *(target INR 2-3)*

- **Major exclusion criteria**
  - Mechanical prosthetic valve
  - Severe renal insufficiency
  - Need for aspirin plus thienopyridine
Stroke (ischemic or hemorrhagic) or systemic embolism

Apixaban 212 patients, 1.27% per year
Warfarin 265 patients, 1.60% per year
HR 0.79 (95% CI, 0.66–0.95)
p (superiority)=0.01

21% RRR
0.5% ARR

P (non-inferiority)<0.001

HR 0.79 (95% CI, 0.66–0.95)
p (superiority)=0.01

No. at Risk
Apixaban 9120 8726 8440 6051 3464 1754
Warfarin 9081 8620 8301 5972 3405 1768
Apixaban: Major Bleeding

Compared to warfarin
RR 0.69 (0.60-0.80)
AVERROES: Apixaban vs. Aspirin

- Patients with AFib, unsuitable for VKA
- Randomized 5600 subjects
  - Apixaban 5 mg twice daily
  - ASA 81-324 mg daily
**Cumulative Risk**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>2791</td>
<td>2720</td>
<td>2541</td>
<td>2124</td>
<td>1541</td>
<td>626</td>
<td>329</td>
</tr>
<tr>
<td>Apix</td>
<td>2809</td>
<td>2761</td>
<td>2567</td>
<td>2127</td>
<td>1523</td>
<td>617</td>
<td>353</td>
</tr>
</tbody>
</table>

**RR = 0.46**

95% CI = 0.33-0.64

p < 0.001

**Stroke or Systemic Embolism**

**Preliminary Results**
Apixaban: Major Bleeding

Compared to aspirin
RR 1.14 (0.74-1.75)
Apixaban

• In patients unsuitable for VKA:
  – Apixaban reduced stroke by ~50% compared to aspirin
  – Without a significant increase in major bleeding

• In patients suitable for VKA:
  – Apixaban reduced stroke by about 20% compared to warfarin
  – With about 30% less major bleeding
Edoxaban

- AFib and at moderate-to-high risk for stroke
- Randomized 21,105 subjects
  - Edoxaban 60 mg (high) or 30 mg (low dose) once daily
  - Warfarin to INR 2.0-3.0

- Primary Outcome: stroke and systemic embolism
Edoxaban—Stroke or Systemic Embolism

A Stroke or Systemic Embolic Event

Hazard ratio and 97.5% confidence intervals
High-dose edoxaban vs. warfarin, 0.87 (0.73–1.04); P=0.08
Low-dose edoxaban vs. warfarin, 1.13 (0.96–1.34); P=0.10

Patients with Event (%) vs. Years
Edoxaban: Major Bleeding

Compared to warfarin:
RR 0.80 (0.71-0.91)     RR 0.47 (0.41-0.55)
DOAC Reversal

FDA Approves Praxbind® (idarucizumab), Specific Reversal Agent for Pradaxa® (dabigatran etexilate)

- First FDA approval of a specific reversal agent for a novel oral anticoagulant (NOAC)
- Praxbind® immediately reverses the anticoagulant action of dabigatran

A Dilute Thrombin Time in Group A

U.S. FDA Approves Portola Pharmaceuticals’ Andexxa®, First and Only Antidote for the Reversal of Factor Xa Inhibitors

A Rivaroxaban (N=26)

<table>
<thead>
<tr>
<th>Time of Blood Sample</th>
<th>Baseline</th>
<th>End of Bolus</th>
<th>End of Infusion</th>
<th>4 Hr</th>
<th>8 Hr</th>
<th>12 Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>0</td>
<td>10-30 min</td>
<td>1 hr</td>
<td>2 hr</td>
<td>4 hr</td>
<td>12 hr</td>
</tr>
</tbody>
</table>

Median

Percent Change (95% CI)

Baseline: 277.0
End of Bolus: -89 (-58 to -94)
End of Infusion: -86 (-55 to -93)
4 Hr: -39 (-27 to -45)
8 Hr: -49 (-43 to -57)
12 Hr: -64 (-51 to -70)
Cautions/Uncertainties

• No need to monitor = no way to monitor
• No need to monitor = less interaction with patients
• Thrombolysis?
• Uses or indications beyond Afib and VTE?
Which DOAC?

- Cost/insurance
- Tolerability

Dabigatran (Pradaxa)
- Twice daily
- Reversal agent widely available
- Cannot be crushed

Rivaroxaban (Xarelto)
- Once daily

Apixaban (Eliquis)
- Twice daily
- Lowest risk of bleeding?
Other Cardioembolic Sources

- Extrapolation of Afib data to other high risk sources:
  - Mechanical prosthetic valve
  - Left atrial/atrial appendage thrombus
  - Sick sinus syndrome
  - Recent myocardial infarction (<4 weeks)
  - Left ventricular thrombus
  - Dilated cardiomyopathy
  - Akinetic left ventricular segment
  - Others?
Anticoagulation for “Low-to-Medium Risk” Sources of Cardioembolism

Mitral valve prolapse
Mitral annulus calcification
Mitral stenosis

Atrial septal aneurysm
Patent foramen ovale

Congestive heart failure

Atrial flutter
Left atrial turbulence (smoke)
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Hypokinetic left ventricular segment
Myocardial infarction (>4 weeks, <6 months)
Embolic Stroke of Uncertain Source (ESUS)

- Stroke detected by CT or MRI that is not lacunar
  - Subcortical infarct ≤1.5 cm (≤2.0 cm on DWI) in largest dimension, and in the distribution of the small, penetrating cerebral arteries.
- Absence of extracranial or intracranial atherosclerosis
  - Causing a ≥50% luminal stenosis in arteries supplying the area of ischemia
- No major-risk cardioembolic source of embolism
  - AF, intracardiac thrombus, prosthetic valve, myxoma/tumors, mitral stenosis, recent MI, EF<30%, vegetation
- No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, drug misuse)

Lancet 2014
ESUS Components

• Truly unexplained ischemic stroke
• Stroke with undetected/occult AF
• Stroke due to “low-to-medium” risk cardiac sources
• Stroke due to arch atheroma
• Stroke due to <50% extra- or intracranial atherosclerosis
What’s in an ESUS?

Nearly identical to cardiogenic emboli.
Anticoagulation For ESUS?
Post hoc subgroups from WARSS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Cryptogenics</th>
<th></th>
<th>hazard ratio (95% CI)</th>
<th>p value2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>proportion with event, % (n)</td>
<td>warfarin</td>
<td>aspirin</td>
<td></td>
</tr>
<tr>
<td>Infarct topography</td>
<td>warfarin</td>
<td>aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial, cortical or cerebellar, large deep (i.e., basal ganglia, etc.), or superficial and deep combined</td>
<td>11.9 (168)</td>
<td>17.8 (170)</td>
<td>0.66 (0.37–1.15)</td>
<td>0.14</td>
</tr>
<tr>
<td>Small deep</td>
<td>14.8 (27)</td>
<td>12.5 (33)</td>
<td>1.17 (0.29–4.69)</td>
<td>0.82</td>
</tr>
<tr>
<td>Brainstem only, brainstem and/or cerebellum</td>
<td>36.8 (19)</td>
<td>10.3 (29)</td>
<td>4.14 (1.07–16.05)</td>
<td>0.04</td>
</tr>
<tr>
<td>No primary lesion on scan</td>
<td>17.5 (57)</td>
<td>17.5 (58)</td>
<td>1.06 (0.44–2.54)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Sacco, 2006
Anticoagulation for ESUS?

- NAVIGATE-ESUS
  - Rivaroxaban vs. aspirin for all ESUS
  - Terminated October 2017 due to lack of efficacy
- RESPECT-ESUS
  - Dabigatran vs. aspirin for all ESUS
  - Results expected October 2018
- ARCADIA
  - Apixaban vs. aspirin for ESUS with “atrial cardiopathy”
  - Launched 2017
Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

Patients with recent ischemic stroke and
1. visualized by brain CT or MRI that is not lacunar (subcortical infarct ≤1.5 cm)
2. absence of cervical carotid atherosclerotic artery stenosis > 50% or occlusion
3. no atrial fibrillation after ≥ 24 hours cardiac rhythm monitoring
4. no intra-cardiac thrombus on echocardiography
5. no other specific etiology for cause of stroke (eg, arteritis, dissection, migraine/vasospasm, drug abuse)

Age ≥ 50 years

459 sites in 31 countries

Study was halted on 5 October 2017 at the 2nd interim analysis at the recommendation of the DMC:
“In the absence of offsetting benefit, and little chance of showing benefit if the study were completed, there is a clear risk of excess bleeding.”
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (N=3609)</th>
<th>ASA (N=3604)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean)</td>
<td>66.9</td>
<td>66.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>62 %</td>
<td>61%</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg (mean ± s.d.)</td>
<td>135.1 ± 17.0</td>
<td>134.9 ± 16.6</td>
</tr>
<tr>
<td>Statin use after randomization</td>
<td>78 %</td>
<td>77 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 %</td>
<td>78 %</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 %</td>
<td>25 %</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>17 %</td>
<td>18 %</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• U.S.A. and Canada</td>
<td>13 %</td>
<td>13 %</td>
</tr>
<tr>
<td>• Latin America</td>
<td>10%</td>
<td>10 %</td>
</tr>
<tr>
<td>• Europe</td>
<td>59 %</td>
<td>58 %</td>
</tr>
<tr>
<td>• East Asia</td>
<td>19 %</td>
<td>19 %</td>
</tr>
<tr>
<td>NIHSS score at randomization (median, IQR)</td>
<td>1.0 (0.0, 2.0)</td>
<td>1.0 (0.0, 2.0)</td>
</tr>
<tr>
<td>Intravenous tPA use</td>
<td>17 %</td>
<td>18 %</td>
</tr>
<tr>
<td>Time from qualifying stroke to randomization</td>
<td>38.0 d</td>
<td>36.0 d</td>
</tr>
<tr>
<td>Intracranial vascular imaging (any type)</td>
<td>78 %</td>
<td>78 %</td>
</tr>
<tr>
<td>Cardiac rhythm monitoring ≥48 hours</td>
<td>34 %</td>
<td>34 %</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Aspirin</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>N (%/yr)</td>
<td>172 (5.1)</td>
<td>160 (4.8)</td>
</tr>
<tr>
<td>HR</td>
<td>1.1 (0.87 -1.3)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.52</td>
<td></td>
</tr>
</tbody>
</table>

Mean follow-up: 11 months
## Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban N=3609 n (%/year)</th>
<th>ASA N=3604 n (%/year)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong> (all recurrent stroke or systemic embolism)</td>
<td>172 (5.1)</td>
<td>160 (4.8)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Individual components included in the primary outcome*

<table>
<thead>
<tr>
<th>Component</th>
<th>Rivaroxaban N=3609 n (%/year)</th>
<th>ASA N=3604 n (%/year)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All recurrent stroke (ischemic, hemorrhagic, undefined)</td>
<td>171 (5.1)</td>
<td>158 (4.7)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>158 (4.7)</td>
<td>156 (4.7)</td>
<td>1.0 (0.81-1.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>13 (0.4)</td>
<td>2 (0.1)</td>
<td>6.5 (1.5-28)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Rivaroxaban
\( N \ (\% / \text{yr}) \)
62 (1.8)

Aspirin
\( N \ (\% / \text{yr}) \)
23 (0.7)

HR 2.7 (1.7-4.4)
\( P = <0.001 \)
## Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban N=3609 n (%/year)</th>
<th>ASA N=3604 n (%/year)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary safety outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ISTH major bleeding)</td>
<td>62 (1.8)</td>
<td>23 (0.7)</td>
<td>2.7 (1.7-4.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Secondary safety outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening/fatal bleeding</td>
<td>35 (1.0)</td>
<td>15 (0.4)</td>
<td>2.3 (1.3-4.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Clinically-relevant non-major bleeding</td>
<td>118 (3.5)</td>
<td>79 (2.3)</td>
<td>1.5 (1.1-2.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>20 (0.6)</td>
<td>5 (0.1)</td>
<td>4.0 (1.5-10.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>- intracerebral hemorrhage</td>
<td>12 (0.3)</td>
<td>3 (0.1)</td>
<td>4.0 (1.1-14.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>- subarachnoid hemorrhage</td>
<td>5 (0.1)</td>
<td>1 (0.0)</td>
<td>5.0 (0.59-43)</td>
<td>0.10</td>
</tr>
<tr>
<td>- subdural/epidural hematoma</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
<td>1.5 (0.25-9.0)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
What rates of ISTH major hemorrhage are anticipated in NAVIGATE ESUS?
(presented to the DMC in March 2016)

• **Rivaroxaban**: Based on RCTs involving older patients with atrial fibrillation, most taking 20mg/d, the major hemorrhage risk was 3% per year. In NAVIGATE ESUS, a lower dose (15mg/d) is tested in younger patients. Estimate **about 2%/yr**. (Vazquez FJ et al. Thromb Res 2016; 138: 1-6)
  
  **Observed**: 1.8%/yr

• **Aspirin**: The major hemorrhage rate in RCTs involving secondary prevention of stroke is **about 1%/yr**. (Haris M et al. Am J Cardiol 2009; 103: 1107-12)
  
  **Observed**: 0.7%/yr

• Anticipated **intracerebral hemorrhage rate** with aspirin: 0.20%/yr.
  
  Observed ICH rate: 0.03%/yr (1/3600 pts x 11 months)
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Rivaroxaban no. of patients with event/total no. (annualized rate)</th>
<th>Aspirin no. of patients with event/total no. (annualized rate)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>172/3609 (5.1)</td>
<td>160/3604 (4.8)</td>
<td>1.07 (0.87–1.33)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yr</td>
<td>43/861 (5.4)</td>
<td>25/855 (3.1)</td>
<td>1.73 (1.06–2.83)</td>
</tr>
<tr>
<td>60–75 yr</td>
<td>90/2019 (4.8)</td>
<td>93/1993 (5.1)</td>
<td>0.94 (0.71–1.26)</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>39/729 (5.7)</td>
<td>42/756 (5.8)</td>
<td>0.97 (0.63–1.51)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>122/2232 (5.8)</td>
<td>102/2204 (4.9)</td>
<td>1.17 (0.90–1.53)</td>
</tr>
<tr>
<td>Female</td>
<td>50/1377 (4.0)</td>
<td>58/1400 (4.5)</td>
<td>0.89 (0.61–1.29)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White only</td>
<td>106/2612 (4.4)</td>
<td>114/2604 (4.7)</td>
<td>0.93 (0.71–1.21)</td>
</tr>
<tr>
<td>Black only</td>
<td>2/51 (3.9)</td>
<td>4/60 (7.9)</td>
<td>0.51 (0.09–2.83)</td>
</tr>
<tr>
<td>Asian only</td>
<td>57/716 (8.3)</td>
<td>34/698 (5.0)</td>
<td>1.65 (1.08–2.52)</td>
</tr>
<tr>
<td>Other</td>
<td>7/230 (3.5)</td>
<td>8/242 (3.9)</td>
<td>0.91 (0.33–2.51)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States and Canada</td>
<td>27/461 (6.4)</td>
<td>15/457 (3.5)</td>
<td>1.82 (0.97–3.42)</td>
</tr>
<tr>
<td>Latin America</td>
<td>12/372 (4.2)</td>
<td>10/374 (3.5)</td>
<td>1.23 (0.53–2.85)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>56/1541 (3.7)</td>
<td>80/1540 (5.4)</td>
<td>0.69 (0.49–0.97)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>24/560 (4.9)</td>
<td>22/558 (4.4)</td>
<td>1.10 (0.61–1.96)</td>
</tr>
<tr>
<td>East Asia</td>
<td>53/675 (8.1)</td>
<td>33/675 (5.0)</td>
<td>1.61 (1.04–2.49)</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Rivaroxaban</td>
<td>Aspirin</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
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<tr>
<td>Estimated GFR</td>
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</tr>
<tr>
<td>&lt;50 ml/min</td>
<td>10/218 (4.8)</td>
<td>11/201 (5.9)</td>
<td>0.86 (0.36–2.02)</td>
</tr>
<tr>
<td>50–80 ml/min</td>
<td>82/1773 (4.9)</td>
<td>97/1758 (5.8)</td>
<td>0.83 (0.62–1.12)</td>
</tr>
<tr>
<td>&gt;80 ml/min</td>
<td>80/1617 (5.5)</td>
<td>52/1644 (3.5)</td>
<td>1.57 (1.11–2.23)</td>
</tr>
<tr>
<td>Stroke or TIA before qualifying stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52/620 (9.2)</td>
<td>51/643 (8.8)</td>
<td>1.05 (0.72–1.55)</td>
</tr>
<tr>
<td>No</td>
<td>120/2989 (4.3)</td>
<td>109/2961 (3.9)</td>
<td>1.09 (0.84–1.42)</td>
</tr>
<tr>
<td>Time from qualifying stroke to randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 days</td>
<td>89/1566 (6.4)</td>
<td>81/1666 (5.4)</td>
<td>1.17 (0.87–1.59)</td>
</tr>
<tr>
<td>&gt;30 days to 3 mo</td>
<td>55/1158 (5.2)</td>
<td>48/1073 (4.9)</td>
<td>1.06 (0.72–1.57)</td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td>28/885 (3.2)</td>
<td>31/865 (3.6)</td>
<td>0.89 (0.53–1.48)</td>
</tr>
<tr>
<td>Cardiac rhythm monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;48 hr</td>
<td>122/2390 (5.6)</td>
<td>103/2382 (4.7)</td>
<td>1.19 (0.91–1.54)</td>
</tr>
<tr>
<td>≥48 hr</td>
<td>50/1218 (4.3)</td>
<td>57/1217 (5.0)</td>
<td>0.87 (0.59–1.27)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>128/2782 (5.0)</td>
<td>121/2803 (4.7)</td>
<td>1.07 (0.83–1.37)</td>
</tr>
<tr>
<td>No</td>
<td>44/827 (5.7)</td>
<td>39/801 (5.2)</td>
<td>1.09 (0.71–1.68)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54/889 (6.8)</td>
<td>46/917 (5.6)</td>
<td>1.21 (0.81–1.79)</td>
</tr>
<tr>
<td>No</td>
<td>118/2720 (4.6)</td>
<td>114/2687 (4.5)</td>
<td>1.02 (0.79–1.33)</td>
</tr>
</tbody>
</table>
NAVIGATE ESUS Main Results- I

- Rigorously-conducted, hypothesis-testing phase III international randomized trial.
- No reduction in recurrent stroke by rivaroxaban 15 mg daily vs. aspirin, and major bleeding was increased.
- Stopped early with 74% of planned primary events, but adequate power to exclude >13% benefit by rivaroxaban.
- High rate of recurrent stroke (~5%/yr) with either treatment.
NAVIGATE ESUS Main Results - II

• “A beautiful hypothesis slain by ugly facts.”*

• Atrial fib identified in 3%; while under-detected, unlikely to be frequent because results were negative.

• Why was NAVIGATE ESUS negative?
  – Did ESUS criteria define embolic strokes?
  – Heterogeneous embolic sources with different composition of emboli did not respond better to factor Xa inhibition?

• Ongoing randomized trials testing alternative anticoagulants will clarify whether the ESUS construct has value beyond identifying cryptogenic stroke patients with high risk of stroke recurrence.

* Adapted from Thomas Huxley; address to British Association for Advancement of Science (1870).
Why Did NAVIGATE Fail?

• Four D’s equals one F
  – Design—Is the ESUS concept dumb?
  – Drug—Wrong drug, wrong dose, need for dual agent (aspirin)?
  – Doctors—Enrolled the wrong patients?
  – DSMB—Did they abort too soon?
NAVIGATE: Rivaroxaban vs. Aspirin with PFO

PFO present: HR 0.54 (0.22-1.36)
### Meta-analysis: Anticoagulation vs. Antiplatelet

#### Table

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Anticoagulation</th>
<th>Antiplatelet</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICSS 2002</td>
<td>2 Events 42 Total</td>
<td>8 Events 56 Total</td>
<td>0.30 [0.06, 1.49]</td>
<td>2002</td>
</tr>
<tr>
<td>CLOSE 2017</td>
<td>3 Events 187 Total</td>
<td>7 Events 174 Total</td>
<td>0.39 [0.10, 1.53]</td>
<td>2017</td>
</tr>
<tr>
<td>NAVIGATE 2018</td>
<td>7 Events 182 Total</td>
<td>12 Events 197 Total</td>
<td>0.62 [0.24, 1.60]</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>411 Total</strong></td>
<td><strong>427 Total</strong></td>
<td><strong>0.48 [0.24, 0.96]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events**: 12, 27

**Heterogeneity**: Tau² = 0.00, Chi² = 0.69, df = 2 (P = 0.71); I² = 0%

**Test for overall effect**: Z = 2.07 (P = 0.04)

---

**OR 0.48 (0.24-0.96); p=0.04**

No evidence of heterogeneity
**ARCADIA Hypothesis**

- **Atrial cardiopathy can cause thromboembolism even in the absence of AF**
  - AF is a common manifestation of atrial cardiopathy but is not necessary to cause thromboembolism
  - Other atrial dysrhythmias associated with stroke even without AF:
    - Frequent PACs -> 2-fold higher risk of stroke
  - Enlarged left atrium potential source of embolism
  - Large p wave negative terminal force indicator of left atrial stress

APEX—Betrixaban FXa Inhibitor

Patients hospitalized with an **acute medical illness (heart failure, infection, stroke)** randomized to oral betrixaban for 35-42 days (n=3,759) vs. subcutaneous enoxaparin for 10 days (n=3,754)

**Results**
- Significant reduction in composite of symptomatic and asymptomatic VTE
- Major bleeding: 0.7% versus 0.6% (p=0.55)

**Conclusions**
- Betrixaban superior to enoxaparin in preventing thrombotic complications
- Bleeding was similar between the groups
- Role in stroke prevention intriguing

Betrixaban—Broad Applications?

Also 47% relative reduction in new ischemic stroke!

RR 0.53 (0.30-0.94)
Large Vessel Disease

- Aortic arch
- Carotid artery (extracranial)
- Vertebral artery (extracranial)
- Intracranial arteries (carotid siphon, MCA, ACA, PCA, Vertebral, Basilar)
Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Harriet Howlett-Smith, R.N., Barney J. Stern, M.D., Vicki S. Hertzberg, Ph.D., Michael R. Frankel, M.D., Steven R. Levine, M.D., Seemant Chaturvedi, M.D., Scott E. Kasner, M.D., Curtis G. Benesch, M.D., Cathy A. Sila, M.D., Tudor G. Jovin, M.D., and Jose G. Romano, M.D., for the Warfarin–Aspirin Symptomatic Intracranial Disease Trial Investigators®
ARCH Trial

- 7.6% of ASA/clopidogrel vs. 11.3% warfarin
- OR 0.76 (0.36-1.61), p=0.50 → Inconclusive
- More vascular death with warfarin
Anticoagulation For Large Artery Disease?

Intracranial stenosis (WASID)

Aortic arch atheroma (ARCH)
Anticoagulation for Large Artery Disease?
COMPASS: Rivaroxaban, Aspirin, or Both:
Prevention of MI, Stroke, or Cardiovascular Death in Patients with CAD or PAD (included carotid disease)
COMPass Primary Outcome
CV death, stroke, or MI

Combination HR 0.76 (0.66-0.86) vs. ASA alone
Secondary: Ischemic stroke HR 0.51 (0.38-0.68)
Is this PRIMARY prevention for stroke?
Newer than NOAC

• Factor X1a inhibition
  – Small molecule and antibody strategies

• Why is XI different?
  – Mutants
    • Rare in general population but 0.2%-9% in some groups
    • No or minimal bleeding but elevated PTT
    • Low risk of cardiovascular and thromboembolic events

Cardiovascular events HR 0.57 (0.35-0.93)
VTE 0.26 (0.08-0.64)
## Short Term Risk after TIA / Minor Stroke

<table>
<thead>
<tr>
<th>ABCD² score</th>
<th>Patients (%)</th>
<th>% risk at 2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>1628 (34%)</td>
<td>1.0%</td>
</tr>
<tr>
<td>4-5</td>
<td>2169 (45%)</td>
<td>4.1%</td>
</tr>
<tr>
<td>6-7</td>
<td>1012 (21%)</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

*Figure: Short-term risk of stroke by ABCD² score in six groups combined (n=4799)*
DATAS II Protocol

300 Patients, NIHSS 0-9, MRI, Randomized <72 h from Onset

Key Exclusion Criteria:
1. DWI volume <25 ml
2. No OAC indication
3. No revascularization procedure planned

Dabigatran 150/110 mg BiD x 30 days

Day 30: MRI and clinical assessment

Hemorrhagic Transformation (Primary Endpoint)

Day 90: Clinical Assessment

ASA 81 mg OD x 30 days

Day 30: MRI and clinical assessment

DWI

Recurrent Infarction

Day 90: Clinical Assessment
### Secondary Outcome: Recurrent Infarcts

<table>
<thead>
<tr>
<th>Intention To Treat</th>
<th>Dabigatran (142)</th>
<th>ASA (142)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Infarct on Day 30 MRI n (Proportion)</td>
<td>9 (6.3%)</td>
<td>14 (9.9%)</td>
<td>0.64 (0.29, 1.44)</td>
</tr>
</tbody>
</table>

**Baseline DWI** → **Day 30 DWI**

- **Dabigatran**
  - 0.9 ml

- **ASA**
  - 0.1 ml
**Primary Outcome (Safety)**

**Symptomatic HT:**
1. >30% of the infarcted area on DWI (PH2)
2. ≥4 point increase NIHSS
3. <5 weeks of randomization

<table>
<thead>
<tr>
<th>On Treatment</th>
<th>Dabigatran (151)</th>
<th>ASA (150)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Hemorrhagic Transformation</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Parenchymal Hemorrhage</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Dabigatran did not increase the rate of symptomatic Hemorrhagic Transformation relative to ASA.
### Incident MRI Hemorrhagic Infarction Type 1

**On Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (141)</th>
<th>ASA (142)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Infarction (%)</td>
<td>11 (7.8%)</td>
<td>5 (3.5%)</td>
<td>2.22 (0.79, 6.21)</td>
</tr>
<tr>
<td>Hemorrhage Volume (ml ± SD)</td>
<td>0.22 ± 0.11</td>
<td>0.34 ± 0.28</td>
<td>0.12 (-0.08, 0.32)</td>
</tr>
</tbody>
</table>
Anticoagulation for Stroke Prevention 2018

- Anticoagulation for AF ✓
- No anticoagulation for ESUS
  - Atrial cardiopathy a new target? Enroll in ARCADIA!
- Low dose anticoag + ASA for CAD and PAD including asymptomatic carotid disease but not stroke
- Evolving landscape
  - Acute therapy, hospitalized patients, large vessel disease, factor XI inhibitors, ...